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REVIEW

Cognitive impairment in chronic obstructive pulmonary disease: disease burden, determinants and possible future interventions

Martijn van Beers [a], Daisy J. A. Janssen[b,c], Harry R. Gosker[a] and Annemie M. W. J. Schols[a]

[a]Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, The Netherlands; [b]Department of Research & Education, CIRO, Centre of Expertise for Chronic Organ Failure, Horn, The Netherlands; [c]Centre of Expertise for Palliative Care, Maastricht University Medical Centre+, Maastricht, The Netherlands

ABSTRACT

Introduction: Cognitive impairment (CI) is an important but an under-recognized extra-pulmonary feature of chronic obstructive pulmonary disease (COPD). It is related to the burden of disability, worse health outcomes, and impaired self-management.

Areas covered: CI includes deterioration of a wide range of cognitive functions, such as memory and various executive functions. Risk of hospitalization might be higher in patients with COPD compared to those without, with CI negatively impacting the wellbeing of patients with COPD. Disease-specific factors such as hypoxemia and inflammation, lifestyle factors such as dietary insufficiencies and lack of physical activity, and comorbidities such as obstructive sleep apnea and depression are likely to synergistically contribute to the development of CI in COPD. Tailored interventions can possibly improve CI in COPD, but this needs further investigation.

Expert commentary: Further research is warranted involving the optimization of neuropsychological testing for screening and outcome assessment, longitudinal studies to investigate the development of CI in COPD over time, and randomized clinical trials to test the feasibility and efficacy of promising interventions.

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COPD; cognitive impairment; pathology

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities [1]. It is well established that common extra-pulmonary comorbidities such as heart failure, osteoporosis, and muscle wasting contribute significantly to the disease burden [2]. Moreover, recent research shows that cognitive impairment (CI) is also a common and important, yet under-investigated comorbidity [3]. This review will discuss various aspects related to CI in COPD: its prevalence and characteristics, related health outcomes, determinants, and possible interventions to maintain or improve cognitive functioning in patients with COPD.

2. Cognitive functioning

Cognition can be defined as any brain function that enables an individual to perceive, register, store, retrieve, and use information in order to adapt behavior to new situations and function in our environment [4]. Cognition consists of many separate domains, including memory, working memory, and attention [5].

Cognition is organized hierarchically and different cognitive functions can be classified as 'lower' or 'higher' [6] (see Figure 1). The lower functions form the basis for the higher functions, including the executive functions such as inhibition (choosing an option that is more rewarding in the longer term instead of the more immediately satisfying option when presented with a choice, for example, refusing the attempt to smoke a cigarette) and cognitive flexibility (being able to swiftly shift mental resources, for example, changing the type of physical activity undertaken in case of weather changes) [7]. Executive functioning in turn underlies even more complex processes such as problem-solving and decision-making, for example, when and how to undertake action in case of increased symptom severity (e.g., disease exacerbation or unintended weight loss).

Specific brain areas do not exclusively perform a single task, but many brain areas are specialized for certain types of tasks (see Figure 2). The language and memory systems are largely located in the temporal lobe, whereas the higher-order functions such as inhibition, cognitive flexibility, reasoning, and decision-making are processed in the frontal lobe. Subcortical structures are located within the brain, including the hippocampus, which plays a central role in memory encoding; the limbic system, including the amygdala and cingulate cortex, which are involved in fear and pain processing; and the basal ganglia, including the caudate nucleus, which is involved in movement but also in learning and remembering [8].

Brain damage, for instance, caused by brain atrophy or degeneration, can contribute to the development of CI. This is an inevitable part of aging, but acute and chronic disease can accelerate it. In the initial stages of CI development,

CONTACT Martijn van Beers martijn.vanbeers@maastrichtuniversity.nl Department of Respiratory Medicine, Maastricht University Medical Centre+, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands

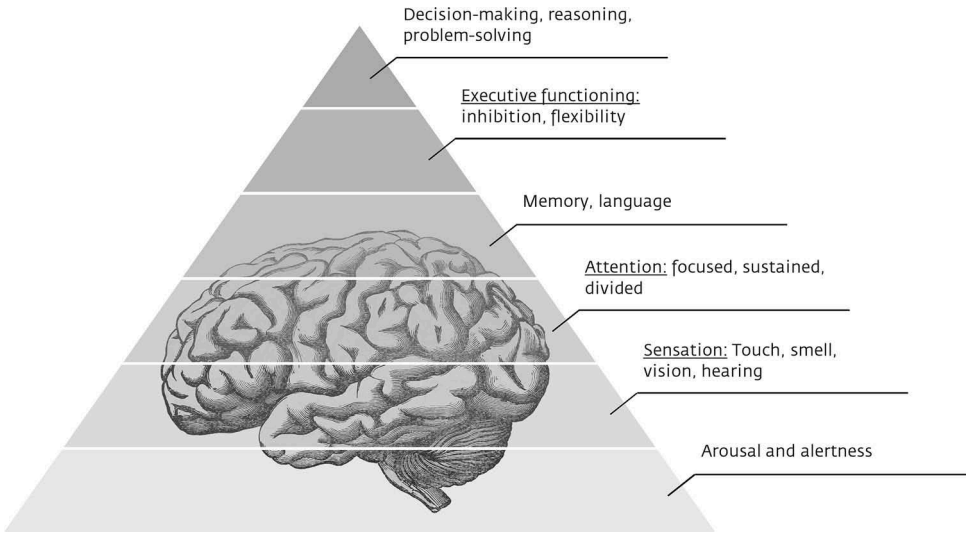

Figure 1. A hierarchical view of cognitive processes. Adapted from Cleutjens et al. [4].

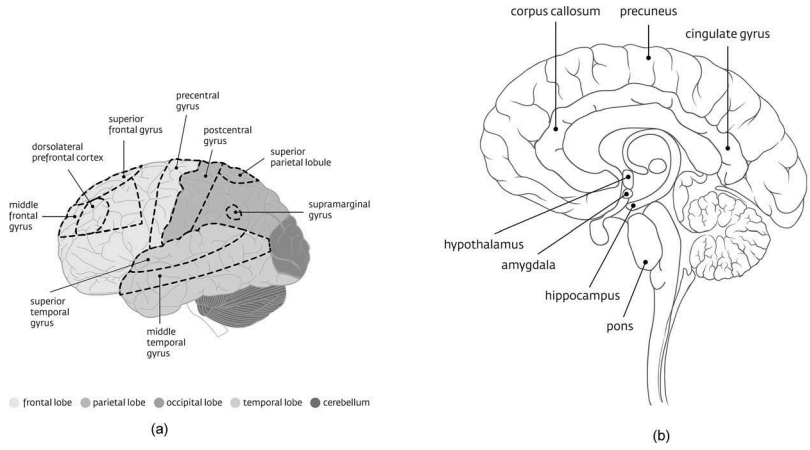

Figure 2. (a) View of the left hemisphere, indicating the areas mentioned in the text. (b) Sagittal view of the brain, indicating the areas mentioned in the text. Adapted from Patrick J. Lynch, medical illustrator, and C. Carl Jaffe, MD, cardiologist.

impairments are noticeable, but not severe enough to impair activities of daily living; a stage called mild cognitive impairment (MCI) [5]. MCI often, but not always, involves impairments in memory rather than in other domains [9], and it may progress into Alzheimer's disease [9] or remain stable [10].

3. Cognitive impairment in COPD

Patients with COPD display impairment in cognitive domains as diverse as attention, executive functioning [3,11–13], (visual) memory and reproduction [14,15], problem-solving, concentration, logical and abstract reasoning, planning, coordination, and organization [3]. Thus, the pattern of impairments is diffuse, and not every patient is affected or suffers from CI to the same degree in different cognitive domains [16]. This diffuse pattern resembles aging-related cognitive deterioration and is consistent with the view of CI in COPD as a manifestation of accelerated aging [3]. On the other hand, patients with Alzheimer's disease or other dementias show a much more specific pattern of CI.

3.1. Prevalence

3.1.1. Cross-sectional studies

A recent meta-analysis pooled 14 studies investigating the prevalence of CI in COPD patients [17]. The average prevalence of any CI (5 studies, $N = 2,995$) was 32%. MCI was present in 25% of patients (11 studies, $N = 4,663$). Higher prevalence of CI was associated with respiratory disease severity, dependence in activities of daily living and poor quality of life [17].

Studies published after this meta-analysis (25 February 2016) show an even higher prevalence of CI (see Tables 1, 2). Two studies by Cleutjens *et al.* reported CI, determined by extensive neuropsychological assessment, in 56.7% and 41.5% of patients with COPD referred for pulmonary rehabilitation (PR) [18,19]. In the former study, only 13.3% of non-COPD age-matched controls suffered from CI. Pierobon *et al.* showed that the Montreal Cognitive Assessment (MoCA) score of 9.5% of patients admitted

Table 1. Overview of studies investigating the prevalence of CI in COPD.

Study (First author, year)	Country	Design	Setting	Population	Sample size	Gender (% male)	Mean age (SD)
Cleutjens, 2017a [18]	Netherlands	cross-sectional	PR	Clinically stable COPD admitted to PR	90	54.4	63.7 ± 8.8
Cleutjens. 2017b [19]	Netherlands	cross-sectional	PR	Clinically stable COPD admitted to PR	76	60.5	62.7 ± 8.7
				non-CI controls with COPD	107	47.7	63.7 ± 9.9
Cleutjens, 2017c [61]	Netherlands	cross-sectional	PR	Clinically stable COPD admitted to PR	157	50.3	62.9 ± 9.4
Lopez-Torres, 2016 [25]	Spain	longitudinal	hospital	Patients hospitalized with and recovering from acute COPD exacerbation	62	75.8	68.32 ± 7.43
Pierobon, 2017 [20]	Italy	observational, cross-sectional	PR	Stable (no exacerbations for the last 3 months) COPD patients with GOLD stage II-IV, group C-D	84	75.0	70.2 ± 7.0
Park, 2018 [27]	USA	observational, longitudinal	NETT	Participants with radiological evidence of bilateral emphysema, severe airflow obstruction and hyperinflation, and the ability to complete PR	307	59.6	66.2 ± 5.7
Roncero, 2016 [21]	Spain	cross-sectional	respiratory medicine department	Ambulatory patients > 40 years with stable COPD	940	81.6	67.6 ± 10.0
Samareh Fekri, 2017 [23]	Iran	cross-sectional	medical university	Patients with a history and symptoms of COPD	87	90.8	60.47 ± 9.83
				Controls without COPD and CI	60	68.33	58.15 ± 9.8

Note. Studies included in the meta-analysis by Yohannes *et al*. [17] are not included in this table. PR: pulmonary rehabilitation; COPD: chronic obstructive pulmonary disease; CI: cognitive impairment; NETT: National Emphysema Treatment Trial; GOLD: Global Initiative for Chronic Obstructive Lung Disease; SD: standard deviation; MAAS: Maastricht Aging Study; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; TMTB: Trail Making Test, part B.

to PR was below the fifth percentile of a normal reference group, and only 38.1% scored higher than the median [20]. This may be related to the fact that patients referred for PR generally have moderate to advanced disease. Roncero *et al*. showed CI in 39.4% of stable COPD patients. This study was large (N = 940), but it only assessed cognition using the Mini-Mental State Examination (MMSE) [21], which is useful as a screening tool but not as a diagnostic tool [22]. Samareh Fekri *et al*. likewise administered the MMSE to 87 COPD patients and 60 age- and gender-matched individuals. MCI was present in 44.8% of patients with COPD and moderate CI in 6.9%, compared to 33.3% and 3.3%, respectively, in controls [23]. It is not reported whether these percentages differ significantly, but the mean MMSE score in the COPD group was significantly lower than in the control group (22.51 ± 2.4 versus 23.63 ± 2.8, respectively).

Lopez-Torres *et al*. investigated cognition during hospitalization for an exacerbation, at discharge and after return to a stable state [25]. Cognitive functioning measured by MoCA scores increased significantly from hospitalization to discharge and decreased again from discharge to stable state, but to a higher level than at hospitalization.

In summary, a wide range of prevalences is reported for CI in COPD. The heterogeneity of applied cognitive tests and cut-off points to define CI, as well as diverse study populations (community-dwelling, pulmonary rehabilitation, hospitalized patients, etc.) likely contributes to this wide range.

3.1.2. Longitudinal studies

Future research using longitudinal designs may elucidate the development of CI in COPD over several years and the influence of disease progression and other factors in different disease stages. The longitudinal studies already conducted have shown some interesting results. A self-reported diagnosis of COPD in midlife increased the risk of developing CI later in life (odds ratio 1.85, 95% CI 1.05–3.28), but COPD diagnosed later in life was non-significantly inversely related to CI (odds ratio 0.30, 95% CI 0.08–1.24) [26]. This surprising result might be explained by survival bias rather than the effects of COPD itself [26]. In a recent study, 32.6% of patients taking part in the National Emphysema Treatment Trial (NETT) were impaired on part B of the Trail Making Test (TMT) at baseline [27]. This test measures task switching, which is part of executive functioning. No prevalence estimates were given for subsequent time points, but TMT-B performance was virtually unchanged over the 3-year follow-up. Most remarkably, the sample could be distinguished into four clusters based on their trajectories of cognitive development over 3 years. One cluster (35.5%) had low baseline TMT-B scores and improving scores over time, the second (39.7%) had low baseline and worsening scores, the third (18.2%) had high baseline and worsening scores, and the fourth (6.5%) had high baseline and improving scores.

Table 2.

Study (First author, year)	Cognitive tests used	Criteria/cut-off for CI	% MCI	% ACI	Misc. methodological strengths/weaknesses
Cleutjens, 2017a	Comprehensive neuropsychological test battery	Score less than 1SD below age-, gender- and education-specific mean of the MAAS study [24] on 2 subtests or more		56.7% (general CI) 13.3% (general CI)	Comprehensive cognitive test battery is used, and cognitive scores are split into different domains. But composite scores are made.
Cleutjens, 2017b	Comprehensive neuropsychological test battery	Score less than 1SD below age-, gender- and education-specific mean of the MAAS study [24] on 2 subtests or more		41.5%	Comprehensive cognitive test battery is used, but composite scores are made.
Cleutjens, 2017c	MMSE; comprehensive neuropsychological test battery	MMSE < 24; Score less than 1SD below age-, gender- and education-specific mean of the MAAS study on 2 subtests or more		MMSE: 5.7% Comprehensive neuropsychological test battery: 38.2%	Comprehensive cognitive test battery is used, and cognitive scores are split into different domains.
Lopez-Torres, 2016	MoCA	MoCA < 20		At exacerbation: 48.3% At discharge: 23.6% In stable condition: 36.3%	Different numbers given for gender and age distribution in table compared with figures. Different MoCA versions were used in order to eliminate practice effects; patients with dementia were excluded from participation.
Pierobon, 2017	MoCA, MMSE	MoCA performance within the bottom 5% of the population		9.5%	Patients with an MMSE of < 18.3 were excluded.
Park, 2018	TMT-B	Score > 1.5 SD above the normative mean of the current study [134.66s for those with < 12 years of education; 81.09s for those with > 12 years of education]		32.6%	In- and exclusion criteria for the NETT trial did not specifically have cognitive research in mind: for instance neurological disorders or medication which could affect cognition were not excluded.
Roncero, 2016	MMSE	MMSE < 27	39.4%		
Samareh Fekri, 2017	MMSE	Mild: MMSE 19–23 Moderate: MMSE 10–19 Severe: MMSE < 10	44.82% 33.33%	6,89% had moderate CI 3.33% had moderate CI	Unconventional cut-offs for CI; skewed gender distribution (91% men in the COPD group); many participants had an opium addiction or history of baking in traditional furnaces; in the control group, a non-smoking history was three times more common than in the COPD group (36.7% vs 12.6%)

3.2. Cerebral abnormalities

CI is associated with global and/or specific cerebral abnormalities, and many studies have found structural or functional abnormalities in patients with COPD, along with elevated serum levels of S100B, a putative marker for brain damage [28].

Cortical degeneration [29–32], increased occurrence of small vessel disease [33] or abnormal functional activation on a global level is uncommon in COPD, with a few exceptions. Two studies found overall increased white matter (WM) lesion volumes and decreased WM integrity [30,31], and cortical thickness and volume were globally reduced in patients who were hospitalized for 30–45 days following an exacerbation [34].

Regional changes are more common. Gray matter (GM) was found to be decreased in many brain regions in both hemispheres, among others in the dorsolateral prefrontal cortex [34], which is involved in higher functions and working memory [35]; different areas involved in visuospatial processing [36]; the frontal cortex; and limbic and paralimbic structures [15,29], which are mainly involved in emotion processing and memory [37]. Disease duration was inversely related to GM volume in various, mainly subcortical, regions [12,29], but not in others, including the hippocampus and amygdala [29].

Reduced WM integrity in the superior and middle frontal gyri and right occipital subcortical WM was shown in patients with moderate COPD [32]. WM integrity was more reduced in the bilateral frontal subcortical areas, right temporal lobe and pons in severe compared to moderate COPD. Patients with an acute exacerbation who had been hospitalized for several weeks also showed reduced WM integrity compared to healthy controls in various (para)limbic regions [12]. However, Cleutjens *et al*. [33] showed that cognitively weak and cognitively strong patients with COPD had equal amounts of WM hyperintensities (WMH).

Two studies investigated the relation between lung function and brain volume in healthy elderly. One study reported a significant correlation between forced expiratory volume in 1 second (FEV_1) and overall brain atrophy and ventricle-to-brain ratio in men but not in women [38]. The FEV_1/forced vital capacity (FVC) ratio was correlated with WMH in the sample as a whole. Participants with and without chronic respiratory disease did not differ on any clinical or brain imaging parameter. Moreover, no control variables were included. The second study only showed a significant positive relationship between FEV_1 and cerebellar WM volume, but no generalized cortical degeneration [39].

The hippocampus is interesting as it is vital in memory formation and learning, and only one of the two regions to display neurogenesis in the adult human brain [40]. As such, decreased hippocampal volume could also indicate abnormalities in brain plasticity in patients with COPD, but findings are mixed. In one study, hippocampal volume was decreased in COPD compared to healthy controls and its size was related to partial oxygen pressure and oxygen saturation [41]. Hippocampal volume did not differ between patients with mild-to-moderate COPD and those with severe COPD [41]. In another study, however, hippocampal volume was not significantly different between patients with COPD and controls [42], and it has also been shown to not differ between cognitively strong and cognitively weak patients with COPD [33].

Functional abnormalities were reported in the left precentral and postcentral gyri and the left caudate nucleus when comparing patients with COPD with controls matched on age, sex, and education [14]. Evidence on resting state network and default mode network activity is mixed. These networks are distinct from others because their activity increases when the brain is not engaged with other tasks [43]. Their increased activation could hinder cognition by interfering with task-related activity. One study found increased resting-state network activity in patients with COPD compared to healthy controls, but this result was not significant anymore after controlling for oxygen saturation [14]. Another study also found increased default network activation in patients with moderate COPD but decreased activation in those with severe COPD [44]. This result might reflect a compensatory response to damage inflicted by factors associated with COPD, and this response might be strongest in patients with moderate COPD [44].

The structural and functional abnormalities discussed above reflect a gradual influence of COPD on the brain. However, COPD can also heighten the risk of more acute events, such as stroke. This is likely due to high levels of systemic inflammation and oxidative stress, possibly as a result of smoking, leading to endothelial dysfunction, decreased vascular reactivity, thickening of the carotid artery wall and atherosclerotic plaque rupture [45]. An elevated risk of stroke in patients with COPD was found in several studies (hazard ratios [HRs] 1.09 [CI95 0.91–1.31] and 1.24 [CI95 1.19–1.28] [46,47]) and meta-analyses (HRs 1.30 [CI95 1.09–2.09] [48,49]). The significance in the latter study was probably due to the large sample size (N = 132,017 versus 1,566 in the former). HRs are roughly equal for the ischemic, hemorrhagic, intracerebral, and subarachnoid hemorrhagic subtypes. However, in the weeks after an acute exacerbation, the HR increased to 6.66 (CI95 2.42–18.20) [46].

In conclusion, patients with COPD show an increased prevalence of many different types of cerebral abnormalities, compared to healthy controls. Patients with COPD have reduced gray and WM volume in various brain areas and WM integrity is compromised. It is still equivocal whether hippocampal volume is decreased in patients with COPD. There is evidence for abnormal functional activation, particularly in the resting state and default mode networks. The abnormalities are spread throughout the brain rather than concentrated in one or some areas. This could possibly explain the diffuse pattern of CI found in COPD.

4. CI and health outcomes in COPD

CI has a wide range of adverse effects on self-management skills and other health outcomes in patients with COPD (see Figure 3).

4.1. Self-management skills

Self-management skills are of major importance for patients with COPD. Symptoms may vary from day to day and increased symptoms may be caused by exacerbations. Patients need to recognize and act upon these exacerbations in an adequate manner [50]. Moreover, patients need to adhere to their

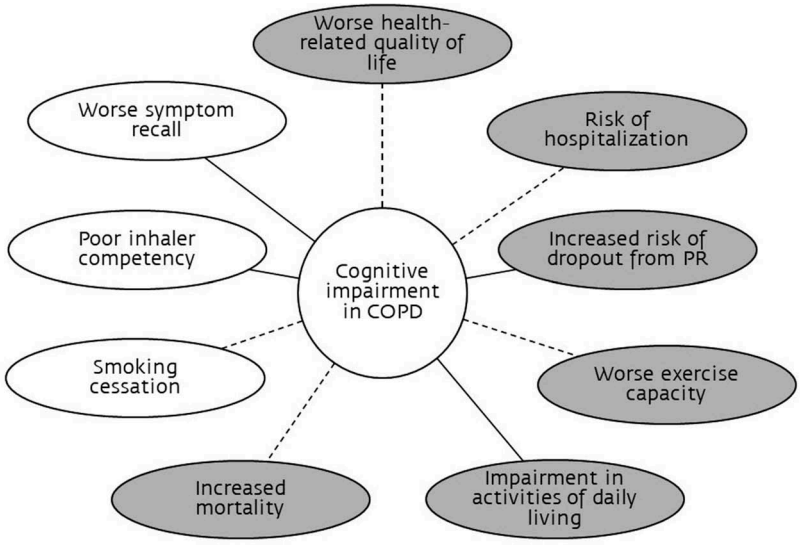

Figure 3. The possible relationships between cognitive impairment and clinical outcomes. Dotted lines represent conflicting literature concerning the relationship.

medication and need to adopt a healthy lifestyle, including a healthy diet and physical activity. Smokers need to quit smoking. This often requires a behavior change, which poses a demand on cognitive functioning [50]. It is therefore feasible that CI limits the ability to cope with the daily challenges of living with COPD.

A recent systematic review revealed that there was just one study in which the impact of CI on self-management skills in patients with COPD was investigated [51]. This particular study, including 100 participants with COPD, showed no relationship between cognitive functioning assessed with the MoCA and overall self-management abilities, as measured by the Self Management Ability Score 30 (SMAS30). SMAS30 assesses the following: taking initiatives, investment behavior, variety, multifunctionality, self-efficacy, and positive frame of mind. Moreover, living alone affected the interaction between cognitive functioning and self-management abilities [52]. In fact, only among patients who lived alone, better cognitive functioning was related to lower self-management abilities [52]. Emotional intelligence (defined as the capacity to understand and manage personal thoughts and feelings, as well as to positively influence interpersonal communication and social well-being), however, seems to be related to self-management abilities in COPD [53].

Meek *et al*. [54] showed a relationship between MMSE scores and the ability to accurately recall severity of fatigue and dyspnea in the previous two weeks. It is reasonable to assume that this might impact on the ability to recognize and act upon symptoms of an exacerbation, but the exact relationship remains unknown.

The relationship between CI and inhaler competency is well-known [51]. An MMSE score of 23–24 points or less is predictive of poor inhaler technique, as are impaired executive functioning and impaired praxis. While some inhalers may be more difficult to use than others, recognizing CI is of major importance when prescribing inhaler devices as well as providing instructions to use them [51]. Some studies suggest Turbohalers might be easier to use for patients with CI than metered dose inhalers [51,55]. To our knowledge, however, there are no recommendations specifically on inhaler use for COPD patients with CI. Nevertheless, inhaler competency is a major consideration when prescribing inhalers and should be checked regularly.

Brega *et al*. [56] showed that older persons with impaired executive functioning were less likely to quit smoking than those with normal executive functioning. However, recent data did not confirm the relationship between executive cognitive dysfunction and smoking cessation [57]. Moreover, another study even showed that persons over 75 years of age who quit smoking had lower cognitive functioning than persons who continued smoking [58]. Differences in findings about the relationship between smoking and cognition might be explained by the fact that patients in the last study were older and different methods were used to assess cognitive functioning. Cleutjens *et al*. did not find a statistically significant difference in smoking status between patients with COPD entering PR with or without CI [19]. Therefore, whether and to what extent CI limits the ability of patients with COPD to quit smoking remains unclear.

4.2. Health outcomes

CI seems related to functional exercise capacity as measured by 6-minute walking distance [59,60]. Nevertheless, this was not confirmed among patients entering PR [19] or during an exacerbation [59].

Cleutjens *et al*. showed that the response after completion of a PR program was similar in patients with CI compared to those without [61]. However, patients with CI were more likely to drop out compared to those without CI (23.3% versus 10.3%, respectively). Therefore, timely recognition of CI in patients entering PR seems paramount.

Several studies showed an inverse relationship between CI and HRQoL as assessed with the COPD Assessment Test [21,60], the EuroQoL-5 dimensions questionnaire [21] or St

George's Respiratory Questionnaire [22]. Then again, other studies did not confirm this relationship [19,62].

The systematic review of Baird *et al*. included four studies exploring the relationship between CI and disability and showed that CI is related to impairment in basic activities of daily living, instrumental activities of daily living, work, and social activities [51]. Martinez *et al*. found that COPD and CI have independent but additive effects on disability [63].

The co-existence of CI and COPD is associated with a more than fourfold increased risk of hospitalization for respiratory-related illnesses and a 34% higher risk of all-cause hospitalization compared to healthy controls, after controlling for various sociodemographic variables, smoking status and comorbidities [64]. Moreover, CI seems to be related to an increased length of hospitalization [22]. Data from the NETT trial did not show an association between impairment in executive functioning and frequency of hospitalization [65].

A study including stable patients with COPD even showed that drawing impairment predicted increased mortality risk [66]. Nevertheless, Yohannes *et al*. found that MMSE scores did not predict 1-year all-cause mortality [67]. Moreover, only a modest association was found between executive function and survival in the NETT trial [65].

In conclusion, CI may negatively impact self-management and health outcomes in COPD, but the current literature is conflicting and many questions remain. The conflicting literature may be explained by different methods used to assess cognitive functioning and criteria used to define CI. Moreover, there were major differences between the studied populations. The complex cause–effect relationships also make this field very challenging. COPD may influence self-management skills, but poor self-management in turn also worsens COPD disease progression, thereby creating a vicious cycle.

5. Determinants of COPD-induced cognitive impairment

Factors such as hypoxemia, hypercapnia, inflammation, and lifestyle factors may all contribute to structural and functional cerebral abnormalities and CI. Any individual factor probably does not explain a significant amount of CI, but their synergistic effects may be large [11,68].

5.1. Hypoxemia and hypercapnia

Hypoxemia and hypercapnia are hallmarks of severe COPD [69] which can also negatively affect cognition [70,71]. Hypoxemia alters the microenvironment around neurons [72] and induces impairments in spontaneous and task-stimulated neuronal activity [73,74]. Hypoxemia might underlie decreases in GM density [12,15], and mild hypercapnia decreases functional connectivity in almost all brain lobes [75]. The exact mechanisms through which this happens are still unclear [75]. Diminished vasodilatation in response to hypoxemia or hypercapnia in patients with COPD might be one [76].

5.2. Inflammation

Multiple lines of evidence indicate that systemic inflammation might underlie CI in COPD. Low-grade systemic inflammation is linked to decreased cognition in other conditions including obesity [77,78] and metabolic syndrome [79,80]. In the general population c-reactive protein (CRP) and interleukin-6 levels were related to global cognition and executive functioning, whereas α1-antichymotrypsin was not [81]. MoCA scores have been found to be negatively correlated with CRP, fibrinogen, and erythrocyte sedimentation rate levels [82]. The relationship between inflammation and cognition in stable COPD has not been thoroughly investigated yet. Next to low-grade systemic inflammation, patients with COPD may experience periods of an enhanced systemic inflammatory response related to disease exacerbations that will be discussed later.

5.3. Respiratory medication

Long-acting beta-adrenoreceptor agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids are frequently prescribed to patients with COPD [1].

Some literature has associated anticholinergic use with increased risk of MCI [83] and dementia [83–85], and faster cognitive decline [86]. However, participants in these studies used systemic rather than inhaled medication. Inhaled medication is much more targeted and will therefore have much less systemic effects. For example, tiotropium cannot cross the blood-brain barrier [87] which might suggest no or limited effect on cognitive functioning. However, no studies have investigated the effects of tiotropium on cognition yet.

The effects of corticosteroids or glucocorticoids (GC) on cognition have not been investigated in patients with COPD yet either. In general, mildly elevated GC levels improve cognition [88], but long-term administration can cause 'steroid dementia', characterized by impairments in episodic, declarative and working memory and executive function, and associated hippocampal and prefrontal dysfunction [89]. Steroid dementia can appear within weeks of commencing GC treatment and is largely reversible upon its termination, although impairments can remain for years after termination [89,90].

It is doubtful whether steroid dementia is a real risk in COPD. The recommended dose and duration for patients with an acute exacerbation (30–40 mg of prednisone daily for 7–14 days, where 5 days may be equally effective [91]) are much lower and shorter than those reported to cause steroid dementia (i.e., 60 mg/day for 7 months [90] or 40–60 mg/day for 37 days [92]).

In conclusion, to date, evidence that respiratory medication can contribute to impaired cognition in patients with COPD is lacking.

5.4. Exacerbations

During acute exacerbations, the above-mentioned determinants intensify and converge. Interestingly, exacerbations

have an additional detrimental effect on cognition [22,82,93,94]. During acute exacerbations, levels of inflammation and cognitive functioning are inversely related [95], and as recovery from exacerbation-related CI seems very slow to non-existent, it can be speculated that regular COPD exacerbations can trigger a stepwise decrease in cognition. One study found no improvement in the 3 months after an exacerbation [22]. However, because these patients were not cognitively tested prior to the exacerbation, it cannot be determined whether the exacerbation actually affected cognition in this study.

5.5. Comorbidities

COPD often presents with comorbid conditions such as obstructive sleep apnea (OSA), depression and chronic heart failure (CHF), and a recent systematic review reported an increased risk prevalence of the metabolic syndrome in COPD compared to matched controls [96].

OSA contributes to decreased arterial oxygen saturation [97], causes sleep fragmentation and cortical and sympathetic arousal [97,98], and affects attention, memory, psychomotor speed, visuospatial abilities, constructional abilities, executive functions, and language abilities [97,99]. Hypoxemia, a shared component between OSA and advanced COPD, might underlie the cognitive deficits apparent in both diseases, namely attention, memory, executive function, psychomotor function, and language abilities [99].

Depression is associated with decreased cognitive functioning [100] in COPD, but it probably only predicts 1–2% of the variation in cognition [3]. A study investigating cognitive bias in patients with COPD and healthy controls with and without depression revealed that depressed patients with COPD showed a comparable pattern of bias compared to depressed healthy controls, whereas never-depressed patients showed much less bias [101]. In conclusion, the influence of concurrent COPD and depression on cognition is still equivocal.

Many patients with COPD also suffer from CHF, and *vice versa* [17]. The prevalence of CI in CHF is largely unknown, as prevalence estimates between 13.5% and 80% have been reported [17]. CHF and COPD might have additive effects on cognition. Moreover, COPD and CHF are both associated with a high prevalence of cerebrovascular diseases, which could lead to chronic cerebral hypoxia, impaired brain perfusion and ultimately brain damage and cognitive impairment [17]. Furthermore, etiological similarities, such as cigarette smoking, may lead to a common set of symptoms, including CI [17].

Metabolic syndrome (MetS) is a cluster of metabolic risk factors, such as central obesity, dyslipidemia, hyperglycemia and dyslipidemia [96], with a prevalence of 34% in patients with COPD [96]. MetS is strongly related to the risk of developing type 2 diabetes and cardiovascular disease [96] and has also been shown to have a deleterious influence on cognition [102,103]. However, some research also suggests that certain components of MetS have a larger effect than others [104,105]. It is yet unclear what the relative contribution of each of the components of MetS on cognition is.

5.6. Smoking

Smoking is one of the largest risk factors for developing lung cancer or COPD, and it affects cognition in multiple ways. Firstly, it increases carbon monoxide and carbon dioxide levels in the blood, causing hypercapnia [106] and hypoxemia [107], respectively. Secondly, cigarette smoke contains many neurotoxic components, such as cadmium, nitric oxide and lead [108]. Thirdly, the many free radicals in cigarette smoke are neurotoxic [109]. And finally, chronic nicotine administration increases tau phosphorylation, a key component of Alzheimer's disease pathophysiology [108], and induced free radical production and depleted antioxidant levels in a rat model [110]. Ultimately, all of these components cause decreased GM and WM volume and connectivity, and impair cognition [111–113].

Only one study investigated the influence of smoking on CI specifically in patients with COPD [114]. Cognitive performance of patients with COPD was comparable to that of smokers, but both were significantly worse compared to normal reference values. The number of pack-years and the duration of abstinence of the past smokers, consisting almost two-thirds of the sample, was not reported. Therefore, it cannot be determined with certainty to which degree smoking affects cognition beyond the effects of COPD. In general, smoking per se contributes to cognitive dysfunction, but there is also evidence of a relationship between impaired lung function and cognition independent of smoking [3,115].

5.7. Dietary insufficiencies

Diet and nutritional habits significantly impact on brain fitness, mental and cognitive health throughout life [116,117]. The relative abundance of specific dietary nutrients, depending on intake, bioavailability and metabolism, affects mental health and cognitive ability via direct and indirect mechanisms that modulate neuronal function and synaptic plasticity [118]. Chronic stress has been shown to negatively impact on brain plasticity and cognitive performance, for instance through the harmful effects of cortisol [119–121] and poor dietary habits are hypothesized to correlate with heightened stress reactivity and susceptibility [122] and greater cognitive decline in elderly [123]. A healthy diet, rich in polyphenols, B vitamins, polyunsaturated fatty acids, and dietary fibers exert favorable effects on cognitive performance, stress reactivity, and neuroinflammation [118,124]. Unintended weight loss and muscle wasting are common in advanced COPD, but specific nutritional deficiencies that could affect cognition have received limited attention to date. However, next to disease severity, Collins *et al*. recently highlighted in a UK COPD population the importance of deprivation on malnutrition risk [125]. An Australian study reported, next to low muscle mass, a high prevalence of deficiencies in vitamin D, vitamin B12 and iron in patients with COPD hospitalized with an acute exacerbation [126]. A Dutch study investigating patients eligible for PR reported that vitamin D and calcium intake were below the recommended levels in more than 75% of patients, whereas vitamin A, C and E intakes were below the recommended levels in over one-third of patients [127]. No studies have yet investigated

the relationship between nutritional status or dietary pattern and cognitive performance in COPD.

5.8. Inactive lifestyle

Higher levels of physical activity are associated with a reduced risk of cognitive decline and dementia [128]. However, disease-related factors such as dyspnea and muscular metabolic abnormalities make it hard for many patients with COPD to be physically active. One systematic review found a mean daily step count of 2,237 [129], which is far less than the threshold for a low active (5,000 steps) or active lifestyle (10,000 steps) indicated by the same authors [129]. Low physical activity levels and a sedentary lifestyle negatively impact on cognition in the general population [130,131], and as such may contribute to CI in COPD as well.

Overall, disease-specific as well as lifestyle factors may contribute to the development of CI in COPD, but the relative potential synergistic contributions of the individual factors are yet unclear.

6. Possible future interventions

6.1. Cognitive training

Cognitive training can improve cognitive functioning in healthy elderly adults [132,133], and can also improve some cognitive domains in those with MCI [132]. Research into cognitive training specifically for patients with COPD is scarce. One trial attempted to ameliorate cognition in hypoxemic patients with COPD through an intervention aimed at improving attention, learning, and logical-deductive thinking [134]. During the first 2 weeks, the intervention group received group cognitive training, in the four weeks thereafter they received individual training, followed by home assignments two times per week. Booster sessions took place after 3 and 5 months. The control group received usual care and no cognitive training. Some cognitive domains improved in both the intervention and placebo group, but the intervention had no additional effect on cognition.

6.2. Exercise training

Exercise can improve cognition through multiple pathways. It causes an increase in cerebral blood flow [38] and levels of cerebral growth factors such as brain-derived neurotrophic factor [135] and insulin growth factor-1 [136]. These growth factors are involved in many functions which are important for cognition. They influence the rate of differentiation and apoptosis of cerebral cells [137] and regulate long-term potentiation [138] and hippocampal neurogenesis [137]. Multiple previous studies have shown the benefit of exercise on cognition in COPD patients [139,140], and in the study by Park *et al*. the 6-minute walking distance was the only potentially modifiable variable that was related to worsening cognitive functioning over time [27]. The question remains, however, whether these improvements consolidate into the longer term if exercise is discontinued [11].

6.3. Smoking cessation

Given the deleterious influences of smoking on cognition, it is unsurprising that smoking cessation is beneficial. However, its effects on cognitive functioning have only been assessed in the general population. It appears that the number of pack-years negatively affects cognitive functioning, but also that cognitive functioning improves with longer duration of abstinence [141]. This implies that abstinence pays off at any age, with the largest benefits coming to those who stop the earliest. Future research should further investigate the effects of smoking cessation on cognition in COPD in more detail.

6.4. Dietary intervention

Dietary intervention may imply adopting a different dietary pattern or supplementing the habitual diet with specific nutrients. The Mediterranean diet, the Dietary Approach to Stop Hypertension (DASH) diet and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet have been proposed as beneficial to cognition [142–144]. Drastic dietary changes, however, are not likely to be feasible for patients with advanced COPD.

These interventions imply that CI in COPD is not something that patients have to passively undergo, but can be readily applied in daily life. However, more research is needed to assess the feasibility and efficacy of the individual interventions or multimodalities thereof.

7. Conclusion

CI in patients with COPD is a problem with a high prevalence and large consequences, yet it is still under-recognized and under-investigated. More research aimed at unraveling the etiology and appropriate interventions to diminish cognitive decline or treat CI in patients with COPD is needed to benefit the patients as well as their loved ones.

Caregivers should pay more attention to potential CI in their patients, as CI may have large consequences on self-management and health outcomes. In a clinical context, administering a brief screening tool may help in identifying patients who need referral to a specialist for further investigation. These patients also need more time and attention, for instance, while making sure they understand how to properly use their medication.

8. Expert commentary

Technical developments in the field of cognitive neuroscience enable more detailed insight in the *pathophysiology* of CI in COPD. Increasing magnetic resonance imaging resolution allows a more detailed picture of the brain, techniques such as diffusion tensor imaging allow focusing specifically on WM instead of the brain as a whole, and shorter and more effective scanning protocols can make brain imaging more accessible and affordable.

Investigating novel research directions might also be worthwhile. For instance, the synthesis and proper functioning of many neurotransmitters, including the catecholamines, glutamate, aspartate, and perhaps most importantly acetylcholine (as it is widely available in the brain but also the most

important neurotransmitter in the airways) depend on oxygen availability [145]. Hypoxia-based neurotransmitter abnormalities might therefore constitute a third type of cerebral abnormality contributing to CI, next to structural and functional abnormalities. However, this has received scarce research attention to date in the general population, and especially in COPD.

Longitudinal studies are essential for understanding the *causes and consequences* of CI in COPD. They can elucidate the development of cognitive decline in COPD in relation to the development of other potentially relevant variables such as impaired lung function, hypoxia or inflammation. In this way, the relative contributions of disease- and aging-related factors can also be further disentangled.

Interesting *treatment options* for CI in COPD include the potential role of specific nutrients in ameliorating cognition. The Mediterranean diet, which is characterized by a high intake of plant-based foods, moderate-to-high fish and seafood consumption and scarce use of dairy products and meat [142], has earlier been shown to improve cognition in a randomized controlled trial [142]. Furthermore, polyunsaturated fatty acids and polyphenols can ameliorate cognition and have a positive effect on various neurobiological processes [146]. Also, testing potential synergistic effects of combinations of interventions could be worthwhile, such as exercise training and cognitive training.

An important prerequisite for all the above research questions is the choice of the right cognitive test instruments. Often applied screening tools such as the MMSE or MoCA can be useful in a clinical setting to identify patients in need of further neuropsychological assessment and therapy, but cannot give a detailed overview of the exact nature of a person's deficits. Larger, well-defined and evidence-based test batteries are essential in order to get a comprehensive overview of a person's neuropsychological functioning [147].

9. Five-year view

In conclusion, it is important to further investigate the pathophysiology, causes and consequences of CI in COPD in the next 5 years, and to develop tailored intervention strategies. Developments in the fields of cognitive neuroscience and neuropsychology will enable a more detailed picture of the pathophysiology of CI in COPD. Longitudinal studies can pinpoint its determinants and identify its consequences, and much work remains to be done in finding (the most) effective treatments.

Key issues

- Cognitive impairment is an important extra-pulmonary feature of COPD
- A wide range of cognitive functions are affected in patients with COPD, such as memory and various executive functions
- Cognitive impairment has a high prevalence in patients with COPD and is more common in patients with COPD than in age-matched controls.
- Many factors can contribute to the development of brain damage and cognitive impairment in COPD, such as smoking, hypoxemia, inflammation, different comorbidities, dietary insufficiencies, medication use and lack of activity.
- Cognitive impairment has large negative consequences on health outcomes of patients with COPD, including hospitalization.
- Interventions such as exercise training, smoking cessation and dietary improvement are promising to prevent or treat (mild) cognitive impairment.

Future research should focus on investigating aspects such as the longitudinal development of cognitive impairment in COPD and the efficacy of various interventions to prevent and treat it.

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Declaration of interest

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ORCID

Martijn van Beers http://orcid.org/0000-0001-6193-3160

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